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(FILE 'HOME' ENTERED AT 17:46:07 ON 31 MAR 1998)

FILE 'WPIDS' ENTERED AT 17:46:11 ON 31 MAR 1998
L1 0 S 9428152 AND TISSUE SPECIFIC

FILE 'MEDLINE, CAPLUS, CANCERLIT' ENTERED AT 17:46:57 ON 31 MAR 1998
L2 25 S TISSUE SPECIFIC AND REPLICAT? AND CONDITION?
L3 19 DUP REM L2 (6 DUPLICATES REMOVED)
L4 2177 S REPLICATING VECTO? AND SPECIFIC PROMOTER OR SPECIFIC RE
L5 498 S L4 AND TISSUE
L6 13 S L5 AND TARGETED

(FILE 'HOME' ENTERED AT 17:46:07 ON 31 MAR 1998)

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FILE 'MEDLINE, CAPLUS, CANCERLIT' ENTERED AT 17:46:57 ON 31 MAR 1998
L2 25 S TISSUE SPECIFIC AND REPLICAT? AND CONDITION?
L3 19 DUP REM L2 (6 DUPLICATES REMOVED)

L3 ANSWER 2 OF 19 CAPLUS COPYRIGHT 1998 ACS
AN 1996:444161 CAPLUS
DN 125:78558
TI Vectors for **tissue-specific replication**
IN Hallenbeck, Paul L.; Chang, Yung-Nien; Chiang, Yawen L.
PA Genetic Therapy, Inc., USA
SO PCT Int. Appl., 56 pp.
CODEN: PIXXD2
PI WO 9617053 A1 960606
DS W: AL, AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG
AI WO 95-US15455 951128
PRAI US 94-348258 941128
US 95-487992 950607
DT Patent
LA English
AB The invention generally relates to targeted gene therapy using recombinant vectors and particularly adenovirus vectors. The invention specifically relates to **replication-conditional** vectors and methods for using them. Such vectors are able to selectively **replicate** in a target tissue to provide a therapeutic benefit from the presence of the vector per se or from heterologous gene products expressed from the vector and distributed throughout the tissue. In such vectors, a gene essential for **replication** is placed under the control of a heterologous **tissue-specific** transcriptional regulatory sequence. Thus, **replication** is **conditioned** on the presence of a factor(s) that induces transcription or the absence of a factor(s) that inhibits transcription of the gene by means of the transcriptional regulatory sequence with this vector; therefore, a target tissue can be selectively treated. Adenoviral vectors were designed with **tissue-specific** transcriptional regulatory sequences linked to the E1a or E2a genes. Examples of the transcriptional regulatory sequences include promoters for .alpha.-fetoprotein (hepatoma-specific), DF3-mucin enhancer (breast cancer-specific), tyrosinase (melanoma-specific), carcinoembryonic antigen CEA (colon cancer-specific), lung surfactant, and ErbB2.

L3 ANSWER 3 OF 19 MEDLINE DUPLICATE 2
A

> d cit ab 1-8

1. 5,728,379, Mar. 17, 1998, Tumor- or cell-specific herpes simplex virus **replication**; Robert L. Martuza, et al., 424/93.2; 435/172.3, 320.1; 935/22, 32 [IMAGE AVAILABLE]

US PAT NO: 5,728,379 [IMAGE AVAILABLE] L7: 1 of 8

ABSTRACT:
A method for killing tumor cells in vivo entails providing **replication** competent herpes simplex virus vectors to tumor cells. A **replication** competent herpes simplex virus vector, with an essential herpes simplex virus gene which is driven by a tumor-specific or cell-specific promoter that specifically destroys tumor cells and is not neurovirulent. Also, a method for producing an animal model, by ablating a specific cell type in vivo, entails providing **replication** competent herpes simplex virus vectors to the animal. Such a vector, with an essential herpes simplex virus gene driven by a cell- or **tissue-specific promoter**, specifically destroys the target cell type. This method of viral-mediated **gene therapy** employs cell-specific viral **replication**, where viral **replication** and associated cytotoxicity are limited to a specific cell-type by the regulated expression of an essential immediate-early (IE) viral gene product.

2. 5,716,826, Feb. 10, 1998, Recombinant retroviruses; Harry E. Gruber, et al., 435/320.1; 536/23.5, 23.72 [IMAGE AVAILABLE]

US PAT NO: 5,716,826 [IMAGE AVAILABLE] L7: 2 of 8

ABSTRACT:
Recombinant retroviruses carrying a vector construct capable of preventing, inhibiting, stabilizing or reversing infectious, cancerous or auto-immune diseases are disclosed. More specifically, the recombinant retroviruses of the present invention are useful for (a) stimulating a specific immune response to an antigen or a pathogenic antigen; (b) inhibiting a function of a pathogenic agent, such as a virus; and (c) inhibiting the interaction of an agent with a host cell receptor. In addition, eucaryotic cells infected with, and pharmaceutical compositions containing such a recombinant retrovirus are disclosed. Various methods for producing recombinant retroviruses having unique characteristics, and methods for producing transgenic packaging animals or insects are also disclosed.

3. 5,716,613, Feb. 10, 1998, Recombinant retroviruses; Harry E. Guber, et al., 424/93.2; 435/320.1 [IMAGE AVAILABLE]

US PAT NO: 5,716,613 [IMAGE AVAILABLE] L7: 3 of 8

ABSTRACT:
Recombinant retroviruses carrying a vector construct capable of preventing, inhibiting, stabilizing or reversing infectious, cancerous or auto-immune diseases are disclosed. More specifically, the recombinant retroviruses of the present invention are useful for (a) stimulating a specific immune response to an antigen or a pathogenic antigen; (b) inhibiting a function of a pathogenic agent, such as a virus; and (c) inhibiting the interaction of an agent with a host cell receptor. In addition, eucaryotic cells infected with, and pharmaceutical compositions

containing such a recombinant retrovirus are disclosed. Various methods for producing recombinant retroviruses having unique characteristics, and methods for producing transgenic packaging animals or insects are also disclosed.

4. 5,691,177, Nov. 25, 1997, Recombinant retroviruses expressing a protein that converts a pro-drug into a cytotoxic agent; Harry E. Guber, et al., 435/172.3, 69.1, 372 [IMAGE AVAILABLE]

US PAT NO: 5,691,177 [IMAGE AVAILABLE] L7: 4 of 8

ABSTRACT:
Recombinant retroviruses carrying a vector construct capable of preventing, inhibiting, stabilizing or reversing infectious, cancerous or auto-immune diseases are disclosed. More specifically, the recombinant retroviruses of the present invention are useful for (a) stimulating a specific immune response to an antigen or a pathogenic antigen; (b) inhibiting a function of a pathogenic agent, such as a virus; and (c) inhibiting the interaction of an agent with a host cell receptor. In addition, eucaryotic cells infected with, and pharmaceutical compositions containing such a recombinant retrovirus are disclosed. Various methods for producing recombinant retroviruses having unique characteristics, and methods for producing transgenic packaging animals or insects are also disclosed.

5. 5,691,147, Nov. 25, 1997, CDK4 binding assay; Giulio Draetta, et al., 435/7.1, 4; 436/501; 530/300, 350; 536/23.1, 23.5 [IMAGE AVAILABLE]

US PAT NO: 5,691,147 [IMAGE AVAILABLE] L7: 5 of 8

ABSTRACT:
The present invention relates to the discovery of novel proteins of mammalian origin which can associate with the human cyclin dependent kinase 4 (CDK4).

6. 5,656,438, Aug. 12, 1997, CAIP-like gene family; Yen-Ming Hsu, 435/7.1, 7.2; 530/387.9, 388.73, 388.75 [IMAGE AVAILABLE]

US PAT NO: 5,656,438 [IMAGE AVAILABLE] L7: 6 of 8

ABSTRACT:
CAIP polypeptide, nucleic acids, antibodies thereto and uses thereof.

7. 5,650,298, Jul. 22, 1997, Tight control of gene expression in eucaryotic cells by tetracycline-responsive promoters; Hermann Bujard, et al., 435/69.7, 172.1, 172.3, 320.1; 536/23.4, 24.1; 935/6, 10, 36, 47 [IMAGE AVAILABLE]

US PAT NO: 5,650,298 [IMAGE AVAILABLE] L7: 7 of 8

ABSTRACT:
Transgenic animals carrying two transgenes, the first coding for a transactivator fusion protein comprising a tet repressor and a polypeptide which directly or indirectly activates in eucaryotic cells, and the second comprising a gene operably linked to a minimal promoter operably linked to at least one tet operator sequence, are disclosed. Isolated DNA molecules (e.g., targeting vectors) for integrating a polynucleotide sequence encoding a transactivator of the invention at a predetermined location within a second target DNA molecule by homologous recombination are also disclosed. Transgenic animals having the DNA molecules of the invention integrated at a predetermined location in a chromosome by homologous recombination are also encompassed by the invention. Methods to regulate the expression of a tet operator linked-gene of interest by administering tetracycline or a tetracycline analogue to an animal of the invention are also disclosed. The regulatory

system of the invention allows for **conditional** inactivation or modulation of expression of a gene of interest in a host cell or animal.

8. 5,641,748, Jun. 24, 1997, Caip-like gene family; Yen-Ming Hsu, 514/12; 435/7.8; 530/324, 350 [IMAGE AVAILABLE]

US PAT NO: 5,641,748 [IMAGE AVAILABLE] L7: 8 of 8

ABSTRACT:
A substantially pure preparation of a polypeptide, the sequence of which comprises the sequence of a CAIP polypeptide.

1. 5,728,379, Mar. 17, 1998, Tumor- or cell-specific herpes simplex virus replication; Robert L. Martuza, et al., 424/93.2; 435/172.3, 320.1; 935/22, 32 [IMAGE AVAILABLE]

US PAT NO: 5,728,379 [IMAGE AVAILABLE] L10: 1 of 1

ABSTRACT:
A method for killing tumor cells in vivo entails providing replication competent herpes simplex virus vectors to tumor cells. A replication competent herpes simplex virus vector, with an essential herpes simplex virus gene which is driven by a tumor-specific or cell-specific promoter that specifically destroys tumor cells and is not neurovirulent. Also, a method for producing an animal model, by ablating a specific cell type in vivo, entails providing replication competent herpes simplex virus vectors to the animal. Such a vector, with an essential herpes simplex virus gene driven by a cell- or tissue-specific promoter, specifically destroys the target cell type. This method of viral-mediated gene therapy employs cell-specific viral replication, where viral replication and associated cytotoxicity are limited to a specific cell-type by the regulated expression of an essential immediate-early (IE) viral gene product.

1. 5,707,618, Jan. 13, 1998, Adenovirus vectors for gene therapy; Donna Armentano, et al., 424/93.21, 93.2; 435/172.3, 320.1; 514/44 [IMAGE AVAILABLE]

US PAT NO: 5,707,618 [IMAGE AVAILABLE] L11: 1 of 7

ABSTRACT:
The present invention relates to novel adenovirus vectors for use in gene therapy which are designed to prevent the generation of **replication-competent adenovirus** (RCA) during in vitro propagation and clinical use. The invention also provides methods for the production of the novel virus vectors. These vectors maximize safety for clinical applications in which adenovirus vectors are used to transfer genes into recipient cells for gene therapy.

2. 5,698,443, Dec. 16, 1997, Tissue specific viral vectors; Daniel Robert Henderson, et al., 435/320.1; 424/93.21; 435/172.3, 252.3; 514/2, 44 [IMAGE AVAILABLE]

US PAT NO: 5,698,443 [IMAGE AVAILABLE] L11: 2 of 7

ABSTRACT:
Host cell specific adenovirus vehicles are provided for transfecting target host cells. By providing for transcriptional initiating regulation dependent upon transcription factors that are only active in specific, limited cell types, virus replication will be restricted to the target cells. The modified adenovirus may be used as a vehicle for introducing new genetic capability, particularly associated with cytotoxicity for treating neoplasia.

3. 5,698,202, Dec. 16, 1997, Replication-defective adenovirus human type 5 recombinant as a rabies vaccine carrier; Hildegund C. J. Ertl, et al., 424/199.1, 224.1, 233.1; 435/235.1, 320.1; 935/32, 34, 57, 65 [IMAGE AVAILABLE]

US PAT NO: 5,698,202 [IMAGE AVAILABLE] L11: 3 of 7

ABSTRACT:
A method of vaccinating a human or animal against rabies is provided by administering a replication defective recombinant adenovirus containing a complete deletion of its E1 gene and at least a partial deletion of its E3 gene, said virus containing in the site of the E1 deletion a sequence comprising a non-adenovirus promoter directing the replication and expression of DNA encoding a rabies virus G protein, which, when administered to the animal or human in said recombinant virus, elicits a substantially complete protective immune response against rabies virus.

4. 5,646,034, Jul. 8, 1997, Increasing rAAV titer; Michael Mamounas, et al., 435/325, 91.4, 172.3, 320.1 [IMAGE AVAILABLE]

US PAT NO: 5,646,034 [IMAGE AVAILABLE] L11: 4 of 7

ABSTRACT:
Methods, kits and compositions for increasing the titer of rAAV vectors are provided.

5. 5,591,439, Jan. 7, 1997, Recombinant cytomegalovirus vaccine; Stanley A. Plotkin, et al., 424/199.1, 230.1, 233.1; 435/5, 69.3, 172.3, 235.1; 536/23.1, 23.72 [IMAGE AVAILABLE]

US PAT NO: 5,591, [IMAGE AVAILABLE] : 5 of 7

ABSTRACT:
The present invention provides a non-defective adenovirus recombinant expression system for the expression of the HCMV gB subunit and for the expression of non-structural immediate-early exon 4 proteins, said recombinant HCMV-expressing adenovirus being useful as a vaccine.

=> d cit ab 6-7

6. 5,585,362, Dec. 17, 1996, Adenovirus vectors for gene therapy; James M. Wilson, et al., 514/44; 435/172.3, 320.1 [IMAGE AVAILABLE]

US PAT NO: 5,585,362 [IMAGE AVAILABLE] L11: 6 of 7

ABSTRACT:
The present invention comprises an improved adenovirus vector and methods for making and using such vectors. The adenovirus vectors of the present invention retain at least a portion of the adenoviral E3 region, carry a deletion of at least a portion of the adenoviral E1 region. Vectors of the present invention preferably also include an additional deletion to accommodate a transgene and/or other mutations which result in reduced expression or over-expression of adenoviral protein and/or reduced viral replication. The vectors of the present invention further include a transgene operatively-linked thereto. By reducing or eliminating viral replication and viral protein expression, the immune response of the infected host to the virus and viral protein is decreased and persistence of transgene expression can be increased. The adenovirus vectors of the present invention are thus particularly useful in gene transfer and therapy.

7. 5,552,143, Sep. 3, 1996, Recombinant cytomegalovirus vaccine; Stanley A. Plotkin, et al., 424/199.1, 186.1, 230.1, 233.1, 278.1; 435/69.1, 69.3, 172.3, 235.1; 536/23.1, 23.72 [IMAGE AVAILABLE]

US PAT NO: 5,552,143 [IMAGE AVAILABLE] L11: 7 of 7

ABSTRACT:
The present invention provides a non-defective adenovirus recombinant expression system for the expression of the HCMV gB subunit, an immunogenic fragment of the gB subunit, and for the expression of non-structural immediate-early exon 4 proteins, said recombinant

L5 ANSWER 2 OF 3 CAPLUS COPYRIGHT 1998 ACS
AN 1996:761941 CAPLUS
DN 126:26823
TI Gene therapy for tumors using **replication competent** targeted adenoviral vectors
IN Gregory, Richard J.; Huang, Whei-Mei
PA Canji, Inc., USA
SO PCT Int. Appl., 35 pp.
CODEN: PIXXD2
PI WO 9634969 A2 961107
DS W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, NL, PT, SE
AI WO 96-US6199 960502
PRAI US 95-433798 950503
DT Patent
LA English
AB A method of treating cancer comprises administering a **replication competent** adenoviral vector contg. a therapeutic gene and a disease specific gene regulatory region operationally linked to at least one replication gene. The **replication competent** targeted adenoviral vector preferentially replicates in the tumor cells following activation of the tumor specific gene regulatory region, thereby amplifying the effect of the therapeutic gene carried by the **replication competent** adenoviral vector. Thus, a recombinant adenovirus was constructed from wild-type adenovirus 5 (Ad5) by two primary modifications. First, the E1a promoter contained between Ad5 coordinates 355 and 483 was deleted and replaced with a 1.7-kb fragment encoding the .alpha.-fetoprotein enhancer/promoter. Second, the E3 region between Ad5 coordinates 28583 and 30470 was deleted and in its place was inserted the HSV-1 TK gene. The recombinant virus vector, by virtue of its AFP control elements, replicates preferentially in AFP cancer cells, allowing the effect of the therapeutic HSV-1 TK gene contained in E3 to be amplified preferentially in those cells in which the tumor-**specific promoter** is activated. The AFP promoter is activated in hepatocellular carcinomas as well as other cancers; other tumor-specific promoters can be inserted in place of the AFP enhancer/promoter in order to amplify the virus in other tumor types. This invention enables for the first time the targeting of a therapeutic gene for treating cancer using small amts. of viral vectors which selectively replicate to deliver therapeutic dosages of the therapeutic gene.